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EMERGING AREA

Dioxazaborocanes: old adducts, new tricks

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Dioxazaborocanes are boronic adducts obtained by condensation of diethanolamine derivatives with boronic compounds. They were first described in the mid-1950's as a practical way to isolate a boronic adduct. Their use has for a long time been restricted to this purpose for the isolation and characterisation of either a final product or a boronic intermediate. Only recently have they been directly involved in chemical transformations in which they proved equivalent or superior to their acid counterpart. In the meantime they have also been used as protected boronic acids. We wish to show in this report that they will likely represent a fluoride-free alternative to organotrifluoroborate salts and therefore an area of intense development.

Introduction

Organoboron chemistry holds a very specific place in organic synthesis due to the very unique reactivity offered by the particular Lewis structure of the neutral boron. Indeed, the vacant orbital of boron is an electrophilic centre, but once filled, it gives a negatively charged boron moiety which can undergo a wide range of rearrangements based on nucleophilic migration α to boron (1,2-migrations). This general mechanism describes most of the functionalisations of B–C bonds commonly described in many textbooks (Scheme 1),[1–2] and is somehow similar to the borono-Mannich or Petasis reaction,[3–7] as well as the mechanism recently proposed for the protodeborylation of tertiary boronic esters.[8]

Their reactivity has also been exploited in mild catalytic processes involving transition metals such as 1,2-addition to carbonyls[9] and imines,[10] 1,4-addition to electron poor alkenes[11–16] or strained alkenes,[17] S_{N2}' reactions[18] and C–X bond formation.[19–25]

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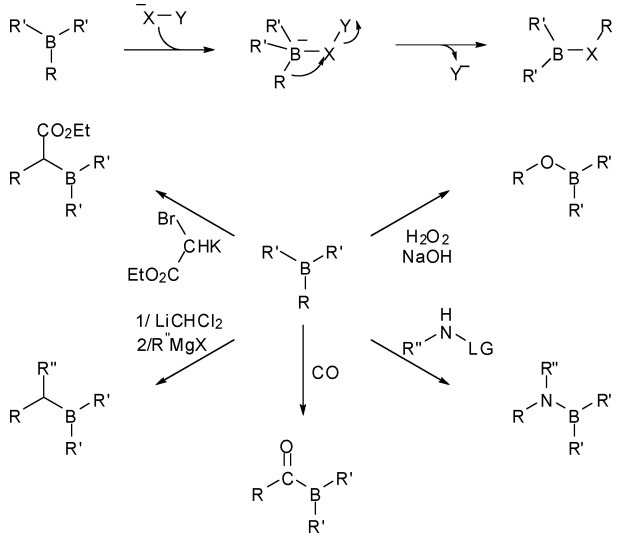
Hélène Bonin

Hélène Bonin was born in Dunkirk, France in 1980. She graduated from the University of Houston and CPE Lyon before moving to Toulouse to work with Emmanuel on dioxazaborocanes and design of palladium catalysts. After getting her Ph.D. in 2009 from the University of Toulouse, she underwent a post doctoral fellowship bridged between the group of Max Malacria at the UMPC Paris and the group of Dennis Curran at the University of Pittsburgh, working on N*-heterocyclic carbene–borane complexes. She will soon undertake a second post doctoral position with Drs Bruneau and Fischmeister in Rennes.*

Thomas Delacroix

Thomas Delacroix graduated from Ecole Supérieure de Chimie Organique et Minérale (ESCOM) in 1997. For his master's degree, he joined the research group of Prof. G. Cahiez then he received his Ph.D. degree in 2001 from the University Pierre et Marie Curie (Paris VI, France) under the supervision of Prof. G. Cahiez. His research focused on the preparation of functionalized organomanganese reagents from organic halides and activated manganese. Then he worked for one year at Rhodia Recherches in Lyon (France) and in Oldbury (UK) within the catalysis department. He's currently process development engineer at Minakem, a fine chemicals/API manufacturer near Lille (France)



Scheme 1 Reactions involving organoboron derivatives.

Obviously the Suzuki–Miyaura reaction appears as one of the most significant applications of organoboron derivatives, mainly implying boronic acid adducts.[26–27] This reaction has become very popular in laboratories and industries because organoboron species are easy to handle, non-toxic and compatible with aqueous solvents. Moreover, yields are usually very high. Both boronic acids and esters are widely described in the literature as nucleophilic partners in carbon–carbon cross-couplings.[28–32]

A lot of boronic acids **1** with a large variety of functionalities are commercially available. However, their purity is rarely high because the corresponding anhydrides are often formed during the isolation process. Boronic acids can indeed undergo dehydration, leading to the corresponding cyclic 6-membered ring anhydrides (so called boroxines **2**), whose partial aromaticity confers an enhanced stability.[33–34] The stoichiometry of the reactants can thus be modified, and the reproducibility of reactions therefore significantly altered. Boronic esters **3** and, more recently, potassium trifluoroborates **4** have thus been used as alternatives to boronic acids (Fig. 1).

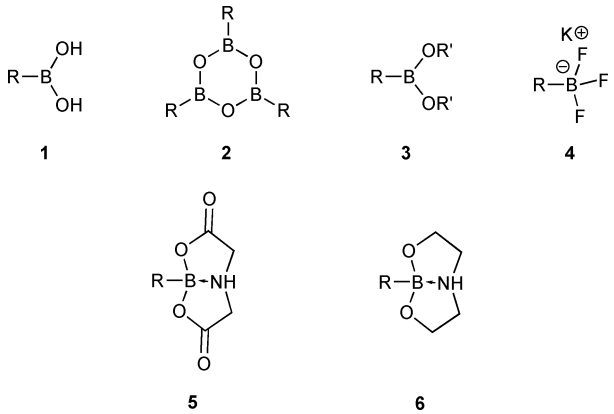


Fig. 1 Structures of various boronic derivatives.

One major advantage of boronic esters is that they cannot be dehydrated to boroxines and when they do not react with air and/or moisture their lower polarity eases their purification by column chromatography.[31,35–37] When chromatography cannot be considered their purification can be tedious, the diols used for their preparation can be expensive, and they are usually less reactive than the corresponding boronic acids. The remaining vacant orbital at boron still represents a limit to their stability (oxidation). Potassium trifluoroborates are negatively charged (or "ate") complexes in which the vacant orbital of the boron atom is filled in with a fluorine atom. They are air- and moisture-stable, and can be used in the same reactions as the corresponding boronic acids with high, and sometimes better, yields.[38–50] The main drawback of these substrates is the use of corrosive KHF_2 and production of a small amount of corrosive and toxic HF during their synthesis. The development of MIDA derivatives **5** by the Burke group has recently brought a new view on organoboronic derivatives. These compounds clearly illustrate that modification of the stereoelectronics around the boron atom has a strong impact on the reactivity of these species. In this case, boronic adducts have been shown to be so stable that they don't even undergo Suzuki–Miyaura cross coupling reactions, extending orthogonal reactivities of boronic derivatives and allowing iterative cross-coupling processes to be achieved.[51–56]

Quite similarly to MIDA derivatives, 1,3,6,2-dioxazaborocanes **6** are boronic esters exhibiting an intramolecular B–N bond.

Obtained by condensation of the very cheap diethanolamine (DEA) with boronic acid (or esters) at room temperature in ethereal solvents, these high melting point solids exhibit an exceptional stability toward heat, air and moisture. Despite their advantages over other organoboron species, such as their ease of synthesis or purification, these compounds have surprisingly not yet been widely used. Through this short review we wish to demonstrate the potential of dioxazaborocanes as interesting alternatives to boronic acids.

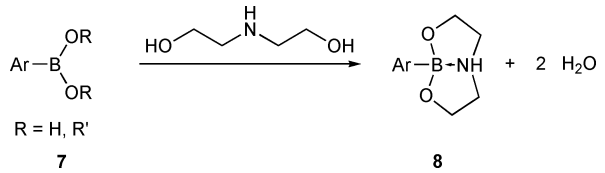
Emmanuel Gras

Emmanuel Gras obtained his Ph.D. in 2000 from the university of Paris XI-Orsay working at the Institut de Chimie des Substances Naturelles in Gif with C. Guillou and C. Thal. After two exciting years of post doctoral fellowship with David M. Hodgson at the University of Oxford he came back to France as "Chargé de Recherche CNRS" at the University of Toulouse. Since 2009, he is working at the Laboratoire de Chimie de Coordination still in Toulouse. His main research focus is to develop practical tools in various fields including organoboron chemistry, asymmetric synthesis, transition metal complexes for catalysis and medicinal (neuro)chemistry.

1. Synthesis, structure and properties of dioxazaborocanes

1.1. Synthesis of dioxazaborocanes

Aryl dioxazaborocanes **8** were first swiftly mentioned in 1955 as crystalline solids.[57–59] They were obtained in high yields by condensation of the non-toxic, non-corrosive and widely available diethanolamine (DEA) on boronic acids (Scheme 2).

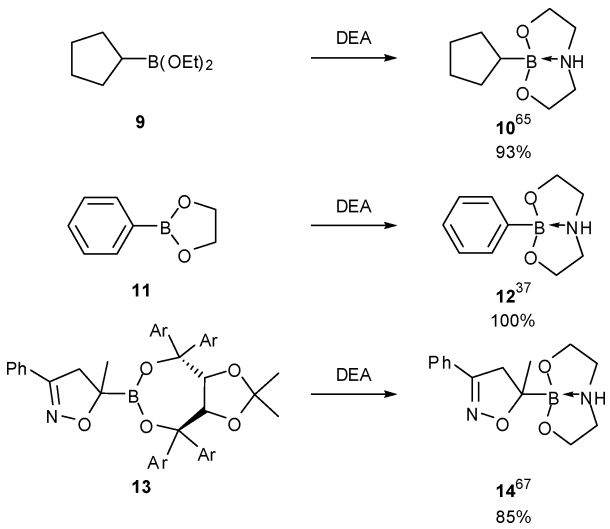


Scheme 2 Synthesis of dioxazaborocanes from boronic acids or ester.

Usually, one equivalent of diethanolamine is added to a solution of boronic acid or ester in solvents such as diethyl ether or dichloromethane. Diethanolamine can be added as a concentrated solution in isopropanol[60] or directly to the solution.[61] In this case, the use of more than one equivalent is usually required due to a poor solubility in non-polar solvents. It is essential to mention that the use of a dehydrating agent or a Dean–Stark apparatus is not required. The same procedure has also been applied to boroxines,[62] alkyl boranes[63] or cycloalkyl diperoxydeboranes obtained by auto-oxidation of alkylborane in the presence of oxygen.[64]

It proved afterward also possible to synthesise dioxazaborocanes from various esters such as diethyl ester **9**,[65] ethylene glycol-derived esters **11**,[37] or pinacol boronic esters.[66] Wallace and Zong also used this method to recover and recycle an optically active diol from **13** (Scheme 3).[67]

Having established this, it appears that dioxazaborocanes can be accessed from boronic derivatives of various origins (Scheme 4). As there is no need to isolate or purify an intermediate boronic



Scheme 3 Synthesis of dioxazaborocanes by transesterification.

acid, potential dehydration or decomposition of the intermediate is thus avoided.

A wide range of dioxazaborocanes (aryl **15–23**,[57,66,68–71] heteroaryl **24–26**,[70,72–73] allyl **28**,[74] primary **27**, secondary or tertiary alkyl **29**[59–60,65,75–79]) can be obtained with a large variety of functionalities (Fig. 2). The condensation of diethanolamine is possible even when sterically-hindered substituents *ortho* to the boronic moiety are present.[69,73,80] Alkynyldioxazaborocanes appear to be the only challenging substrates that have not yet been reported.

One significant advantage of dioxazaborocanes over other boron derivatives is their ease of purification, which makes them as conveniently synthesised as trifluoroborate salts with no fluoride source required. They are, indeed, obtained as pure solids by a simple filtration from ethereal media, since they usually precipitate from the mixture immediately after addition of the diethanolamine, no dehydrating agent being required.[79,81] Further purification by chromatography on silica gel appears

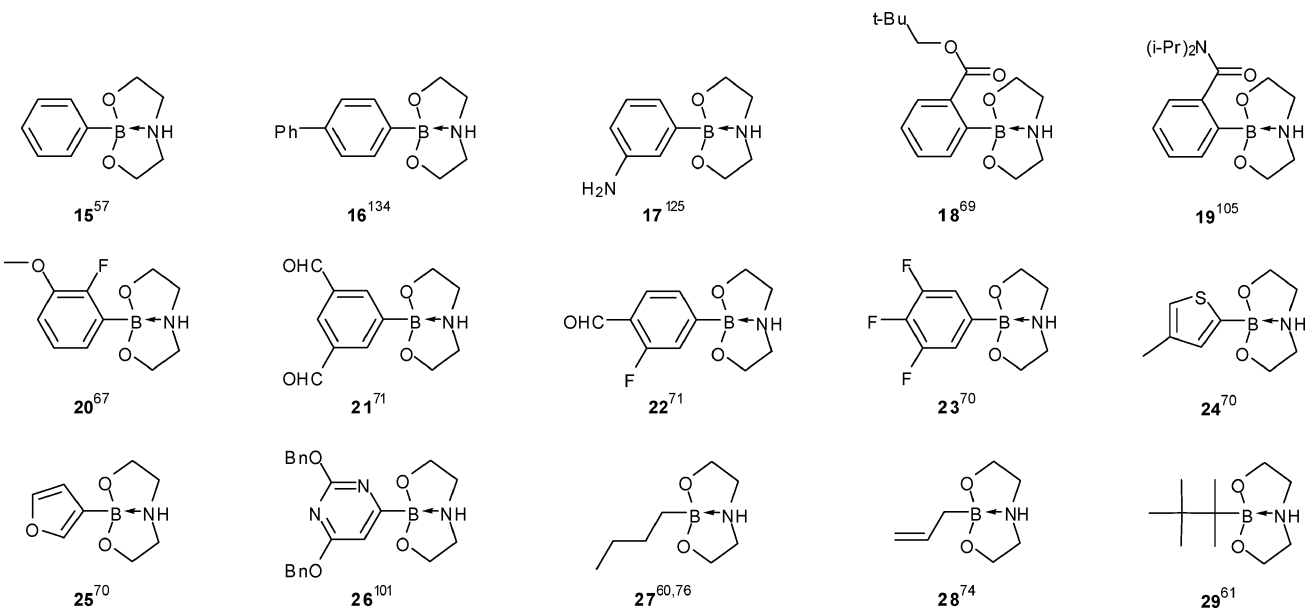
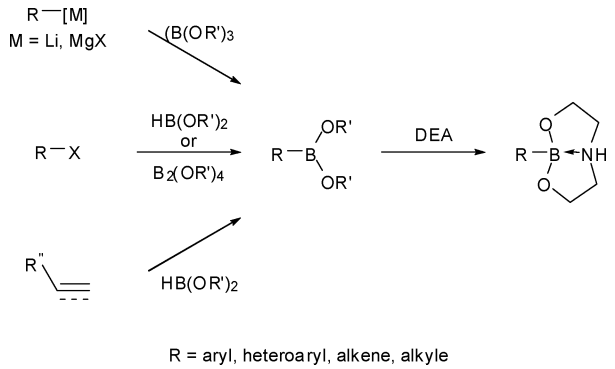


Fig. 2 Selected examples of functionalised dioxazaborocanes.



Scheme 4 Synthetic pathways for the synthesis of dioxazaborocanes.

somehow compromised by the high polarity of dioxazaborocanes. Nevertheless, they can usually be recrystallised from acetone or acetonitrile.

Noteworthily, optically active alkyl derivatives **30–33** have also been described (Fig. 3).[75,82–84] The isolation procedure of these dioxazaborocanes was far better than the one of the corresponding diethyl boronates.

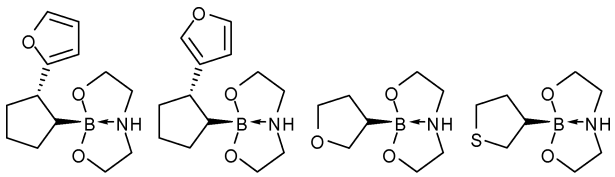
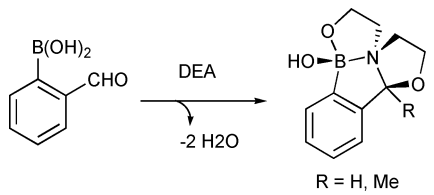


Fig. 3 Selected examples of optically active dioxazaborocanes.

All these examples, which are not fully comprehensive, illustrate the wide generality of accessible dioxazaborocanes. Yet it should be noted that when the boron moiety is located *ortho* to a carbonyl group on an aromatic ring an alternate structure can be isolated.[71] In this case the nitrogen is deprotonated and interacts with the boron atom and the carbonyl to form a tetracyclic structure (Scheme 5).



Scheme 5 Ortho substitution of the boronic moiety by a carbonyl group prevents the formation of the dioxazaborocane.[71]

1.2. Structure of dioxazaborocanes

The interaction between the vacant orbital of boron and the lone pair of nitrogen in dioxazaborocanes was first suggested by Musgrave and Park who observed, by IR spectroscopy, N–H stretching at a low wavenumber value.[58] The observed frequency (at around 3100 cm^{-1}) is significantly lower than is usually observed for secondary amines at 3290 cm^{-1}. Such a lowering of the N–H bond strength was suggested to arise from the development of a positive charge on the nitrogen. Weidmann and Zimmerman also concluded the presence of a N→B interaction by comparing IR spectra of dioxazaborocanes to that of an array of phenyl boroxazolidines. Lowesson carried out similar IR studies on aliphatic dioxazaborocanes at various concentrations and concluded that an intermolecular hydrogen bond was taking place.[59]

This interaction was also studied by ^{1}H and ^{11}B NMR spectroscopy. The ^{11}B chemical shift (relative to $BF_3{\cdot}OEt_2$) of boronic esters is at around 30 ppm whereas the one of dioxazaborocanes is typically around 12 ppm in aprotic solvents, thus indicating a pyramidalization of the boron atom.[63,85] The intermediate ^{11}B chemical shift of dioxazaborocane, lying between the ones of negatively charged boron complexes (generally around 5 ppm) and boronic esters, also supports the presence of a N→B dative bond. Proton spectra confirmed the [3,3,0]-bicyclic structure of the compounds, since geminal protons of the methylene groups become unequivalent, inducing a complex coupling pattern.

X-Ray crystallographic structures of dioxazaborocanes confirmed the transannular N→B bridge and the tetrahedral geometry of the boron atom.[69,77,86–90] They also demonstrated that both hydrogen bonding and N→B interaction exist and contribute to the N–H stretching frequency shift.

The conformation of the two five-membered rings is different. As only one of the oxygens is involved in an intermolecular H-bond with the hydrogen atom borne by the nitrogen, the molecules are linked into spiral chains. The observed dihedral angles in both rings are in the range of those classically observed for cyclopentanes.

In phenyl dioxazaborocanes, the phenyl ring plane generates a slight dihedral angle with the BOO plane. The angles in the aromatic ring range from 116° to 122° (Fig. 4). The α angle has a value of 116°, whereas the β, γ and δ angles exhibit respectively 122°, 120° and 119° values. This small α angle of 116° unsurprisingly indicates that the dioxazaborocane group is electron donating, and thus, that there is a small residual negative charge on the aromatic π-system.

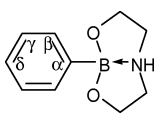


Fig. 4 Angles of the dioxazaborocane aromatic ring.

The B–C bond length, which is about 1.61 Å, is shorter than the ones in sodium tetraphenylborate[91] or in phenyl potassium trifluoroborate,[92] which are around 1.64 Å, thus indicating a stronger bond. The B–N bond length of dioxazaborocanes is about 1.66 Å, whereas a covalent B–N bond length is usually 1.46 Å, again testifying to a dative bond. Finally, the B–O bond lengths lie in the range 1.43–1.47 Å, whereas they are in the range 1.31 to 1.38 Å in trigonal boronic derivatives, in which an interaction takes place between the oxygen lone pairs and boron.

1.3. Stability of dioxazaborocanes

Dioxazaborocanes are extremely stable towards air and moisture. They can be stored at room temperature without any precaution. For instance, Woods, Bengelsdorf and Hunter stored a sample of vinyldioxazaborocane on a bench for more than 4 years without

any noticeable degradation.[93] 2-Pyridyl compounds that could not be isolated as boronic acids or esters[94–95] could be prepared and isolated with high yields and stored as their dioxazaborocane derivatives.[96–98]

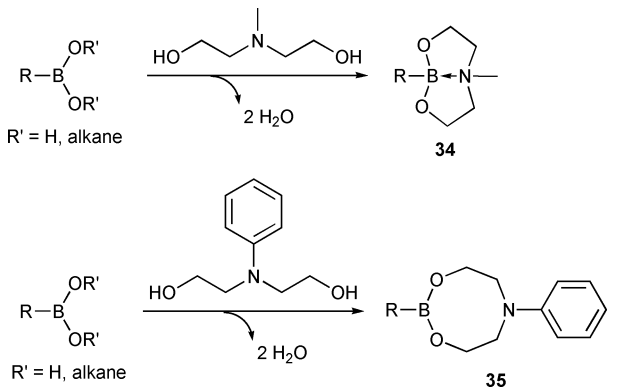
These compounds are not sensitive to oxidation or prone to dehydration. They are stable under basic conditions required for the Suzuki–Miyaura coupling, and the corresponding boronic acids are easily recovered, acidic conditions (pH < 2) driving the diethanolamine in the aqueous phase.[69,99]

In organic solvents, the ^{11}B NMR spectra show only one peak at a chemical shift of around 12 ppm that was assigned to the B–N coordinated tetrahedral species. In water, the appearance of a new species with a chemical shift around 20 ppm could be observed.[100] This chemical shift suggests a weakening or a disappearance of the B–N interaction. Schinazi and Prusoff already observed this phenomenon and suggested the slow decomposition of the compound to the boronic acid and diethanolamine.[101] Still, it should be noted that a simple evaporation of the water regenerates the dioxazaborocane as assumed by the reappearance of the chemical shift at 12 ppm (ruling out a potential formation of boric acid).[100] One can therefore not rule out an equilibrium between a "closed" and an "open" shape and further structural investigations are still required to elucidate the real outcome in the presence of water.

It is noteworthy that alkyl dioxazaborocanes seem to be much more sensitive to water or methanol than aryl derivatives, and it is not clear yet if the same equilibrium happens or if the compounds are hydrolysed or methanolised.[61]

1.4. *N*-Methyl and *N*-phenyl dioxazaborocanes

N-Methyl and *N*-phenyl dioxazaborocanes such as **34** and **35** were also synthesised through similar methods using the corresponding *N*-substituted diethanolamines (Scheme 6).



Scheme 6 Synthesis of *N*-methyl and *N*-phenyl dioxazaborocanes.

N-Methyl derivatives are as stable as the corresponding dioxazaborocanes. They exhibit the same boron chemical shifts around 12 ppm, and an X-ray crystallographic structure showed the pyramidalization of the boron atom.[102] However, most of them are liquids and therefore less easy to purify.[65]

It can be assumed that for *N*-phenyl compounds no interaction takes place between the boron and the nitrogen atoms, as suggested by the ^{11}B chemical shift at $\delta \sim 30$ ppm. This is probably a result of the delocalization of the nitrogen lone pair in the aromatic ring preventing its interaction with the boron vacant orbital. They are thus less stable and of lower interest.[65,98]

2. Applications of dioxazaborocanes

So far dioxazaborocanes have been mainly used to isolate, characterise, immobilise or protect boronic acids. Their use in organic or transition metal-catalysed reactions remains scarce as we will see in the last part of this section.

2.1. Characterization of boronic acids

Dioxazaborocanes were first developed by Letsinger and Skoog to obtain solid derivatives with high and sharp melting points.[57] Boronic acids are usually notoriously difficult to characterise in terms of melting points or elemental analysis because they partially or fully dehydrate quite easily. Conversion of new boron derivatives to the corresponding dioxazaborocanes allows one to get quantitative yields of solids with sharp melting points and correct elemental analysis. Moreover, upon recrystallisation, they usually provide crystals suitable for X-ray crystallographic studies.[69,77,86–90] Dioxazaborocanes are thus very useful to confirm or prove the structure of new boron derivatives.

Their application to the characterisation of boronic acids that cannot be otherwise isolated is nicely exemplified in the case of pyridyl derivatives **36–38**, as described by Fischer and Havinga[103] as well as by Sopkova de Olivera Santos and co-workers (Fig. 5).[96,102]

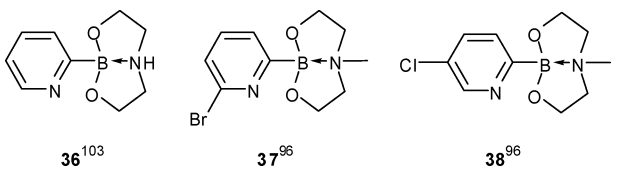


Fig. 5 Selected examples of pyridine dioxazaborocanes.

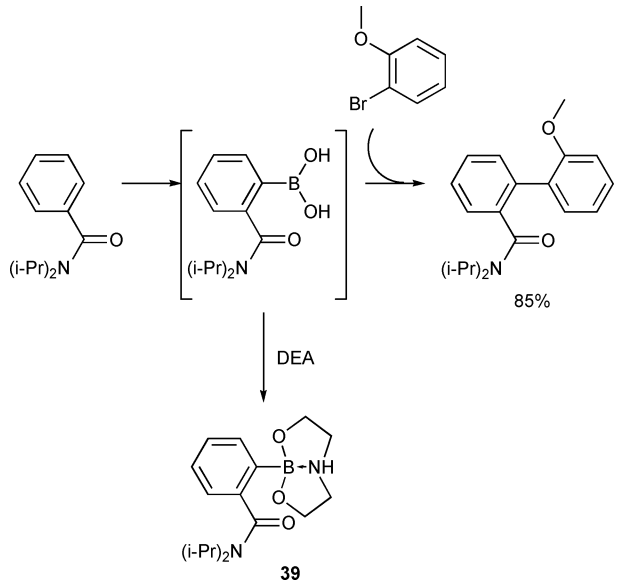
One can also take advantage of the easy and efficient formation of dioxazaborocanes from boronic derivatives to characterise reaction intermediates that are not isolated.[104] This has been exemplified by Snieckus and co-workers who evidenced an intermediate benzamide boronic acid by converting it to the dioxazaborocane **39** (Scheme 7).[105] The unisolated boronic acid was then directly cross-coupled with an aryl bromide.

Brown and co-workers also used this approach and converted the boronic intermediate **40** into **41** to establish the structure of the intermediate **40** in the course of the oxidation process (Scheme 8).[106]

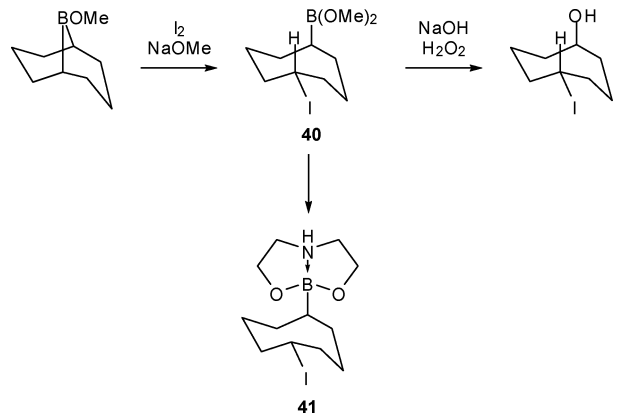
This approach proved efficient for a wide array of compounds including aryl diboronic acids,[107–109] heterocyclic derivatives,[101,110–111] alkyls,[61,75,84,112–113] aryls[69,104–105,114] and alkenes.[115]

2.2. Isolation of a compound from a mixture or purification

The ease of purification of dioxazaborocanes has been used to isolate the desired boronic ester from the reaction mixture, thus allowing one to avoid a workup. Thanks to their low solubility in non-polar solvents, only the diethanolamine ester of the desired compound precipitates from the mixture, leaving most impurities

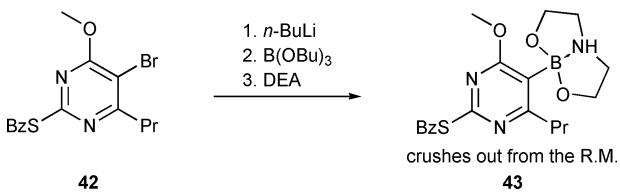


Scheme 7 Characterisation of an intermediate boronic acid as its diethanolamine ester.[105]



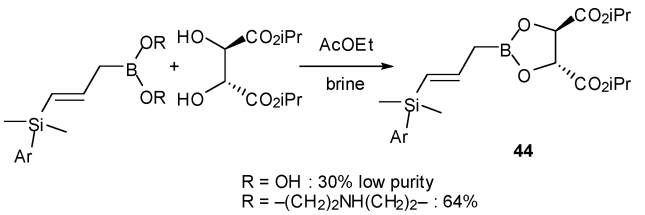
Scheme 8 Characterisation of an intermediate boronic ester as its diethanolamine ester.[106]

in solution. A simple filtration provides a pure compound as exemplified in the isolation of **43** from **42** (Scheme 9).[101,106,115–116]



Scheme 9 Isolation of a boronic ester from a mixture by formation of its diethanolamine ester.[116]

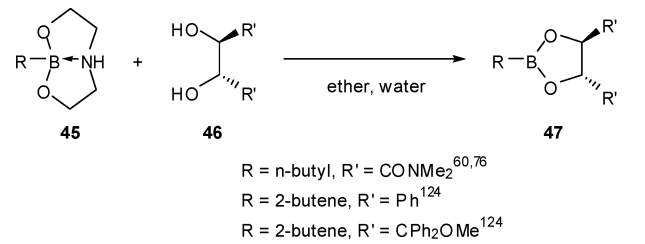
When required, the corresponding boronic acid can then be easily regenerated by a simple hydrolysis. This method was also used to isolate pure boronic acid (used for the synthesis of **44**) from a mixture by precipitation of its diethanolamine ester. Dioxazaborocanes were then immediately hydrolysed in a biphasic mixture, and esterified again with a chiral tartrate derivative. The chiral ester **44** is thus obtained pure with a good yield (Scheme 10).[117] If the esterification is attempted directly with the crude



Scheme 10 Isolation of a boronic acid by formation of its diethanolamine ester followed by hydrolysis and transesterification.[117]

reaction mixture (prior to dioxazaborocane formation), both yield and purity of the product are much lower.

The method has been extended to the formation of chiral boronic esters **47** starting from chiral diols **46** and dioxazaborocanes **45** (Scheme 11).[60,76,118–124] It is noteworthy that the purification of the new chiral boronate is again facilitated as a consequence of a lower load of by-products. Different kinds of chiral esters were obtained using this method, and it should be noted that the presence of water was always mandatory to achieve good transesterification yields.

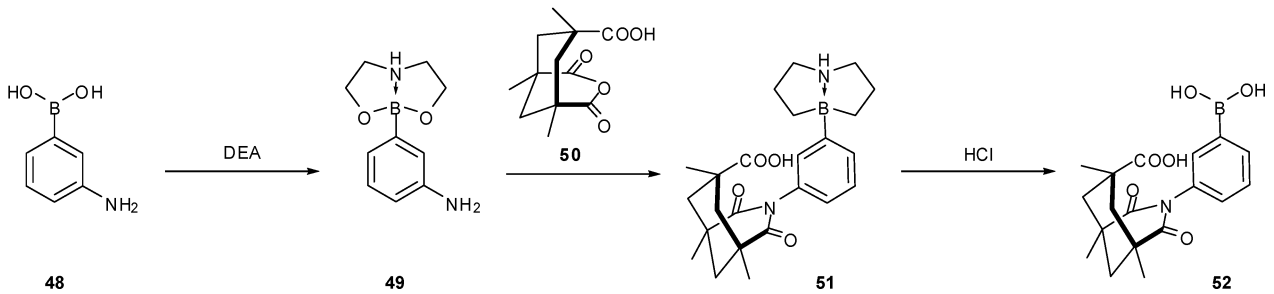


Scheme 11 Selected examples of transesterification of dioxazaborocanes with chiral diols.

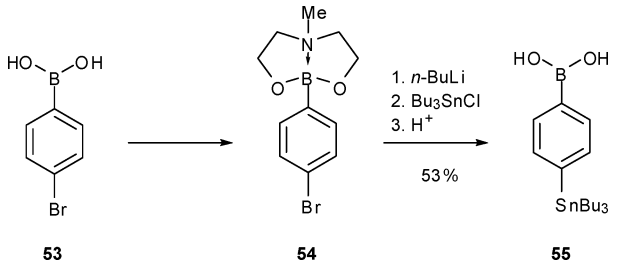
2.3. Protection of the boronic acid function

Another use of dioxazaborocanes is the protection of boronic acid moieties during their functionalisation. In order to synthesise a *meta*-substituted arylboronic acid linked to a carboxylic acid *via* a *U*-shaped spacer **52**, Smith and co-workers exploited the formation of intermediate dioxazaborocanes **49** and **51** (Scheme 12).[125] The 3-aminophenylboronic acid **48** was transformed into the corresponding diethanolamine ester **49**, prior to reaction with the anhydride **50**. It is noteworthy that the anhydride reacts exclusively with the poorly nucleophilic nitrogen of the aniline. Indeed, this somehow shows that a B–N interaction is maintained under the reaction conditions preventing the more nucleophilic secondary amine from reacting with the anhydride. Once the functionalisation is done, the free boronic acid function was restored quantitatively by acidic hydrolysis.

Previously, Yamamoto and co-workers accessed the *para* disubstituted aryl **55** bearing a tin and a boronic acid function (Scheme 13).[126] The boronic moiety was protected with *N*-methyl diethanolamine before treatment of the brominated aryl with n-butyllithium and addition of tributyltin chloride. Acidic work-up allowed the recovery of the bimetallic species with a free boronic acid. In this case a *N*-substituted diethanolamine was required to avoid the use of an excess of n-butyl lithium and potential subsequent difficulties.



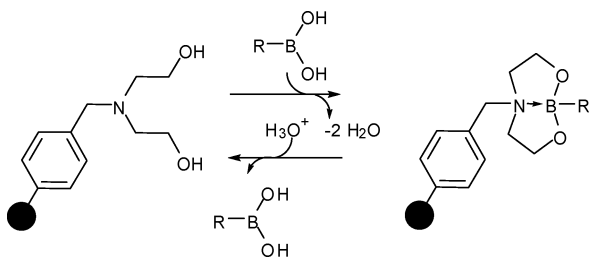
Scheme 12 Protection of a boronic acid moiety by the formation of its diethanolamine ester.[125]



Scheme 13 Protection of a boronic acid moiety during a metallation process.[126]

Protection of the boronic moiety was also used for 1,2-addition to aldehyde,[127] catalytic hydrogenation of benzyl protections,[101] *S*-benzyl group cleavage,[116] or formation of sulfonamide derivatives from brominated compounds.[128–129]

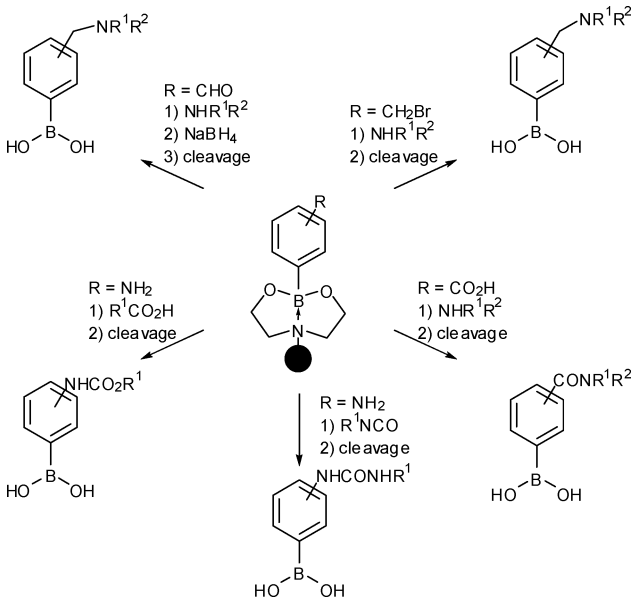
Hall and co-workers described the first synthesis of a *N*,*N*-diethylaminomethyl polystyrene capable of quantitatively immobilizing boronic acids (Scheme 14).[130]



Scheme 14 Dioxazaborocanes for immobilisation and release of boronic acids on a polystyrene polymer.[130]

The stabilizing effect of the B–N interaction could be somehow demonstrated by comparison with the immobilising ability of a glycerol grafted resin. Free boronic acids could then be simply released by acidic or neutral hydrolysis.

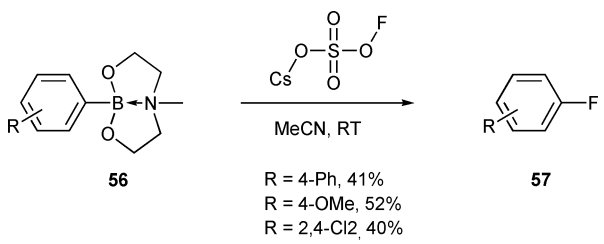
This solid phase immobilisation was used as a protection of the boronic acid moiety to functionalise the substrates.[131–132] The dioxazaborocane moiety was shown to be stable under various reaction conditions including nucleophilic substitution of a halogen by an amine, reductive amination of aryl aldehydes, amidation of benzoic derivatives and reactions of aniline with carboxylates and isocyanates (Scheme 15). Simple acidic or neutral cleavage afforded the desired boronic acids in good yields and purity. This approach proved, therefore, to be a fruitful solid-supported strategy for the synthesis of functionalised boronic acids.



Scheme 15 Protection of boronic acid moieties under various reaction conditions.[131–132]

2.4. Use in organic chemistry

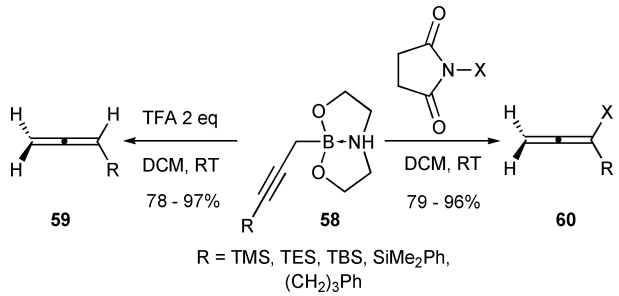
2.4.1. Synthesis of aryl fluorides. Widdowson and co-workers established that treatment of aryl *N*-methyldioxazaborocanes **56** with caesium fluoroxysulfate in the presence of 1,3-dinitrobenzene in acetonitrile converts the former to the corresponding fluoroaromatics (Scheme 16).[133,134] Only moderate yields (15–52%) were achieved, but they remain similar to some obtained from the free boronic acids reported by the same group.[135]



Scheme 16 Fluorodeborylation from *N*-methyldioxazaborocanes.[134]

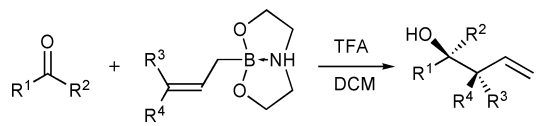
2.4.2. Allene synthesis, allylation and propargylation. Recently, Fandrick and co-workers used propargylic dioxazaborocanes **58** for the preparation of allenes in high yields and

regioselectivities. Protonolysis with TFA yielded the monosubstituted allenes **59**, whereas halogenation with *N*-halosuccinimides gave access to the disubstituted allenes **60** (Scheme 17).[136]



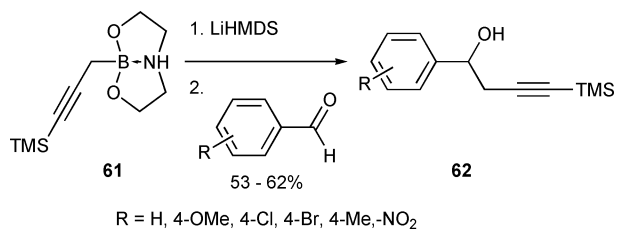
Scheme 17 Synthesis of allenes from propargylic dioxazaborocanes.[136]

Allyl dioxazaborocanes have also very recently been involved in allylation of aldehydes and ketones under mildly acidic conditions (Scheme 18).[137] The diastereospecificities observed during crotyl transfers are consistent with a Zimmerman–Traxler transition state which can be accessed either by oxygen or nitrogen decoordination from boron.



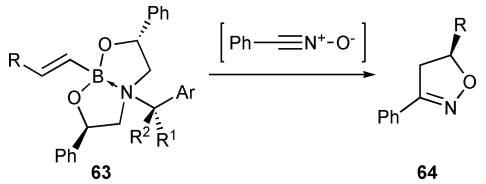
Scheme 18 Diastereospecific allylation with dioxazaborocanes under acidic conditions.[137]

Silylated propargylic dioxazaborocanes **61** were also used for the synthesis of *C*-silylated homopropargylic alcohols **62** from the corresponding aromatic aldehydes with moderate yields (Scheme 19). The nucleophilicity of the propargylic group was enhanced by using LiHMDS to deprotonate the nitrogen of the dioxazaborocane moiety, thus forming an "ate" complex. The basic treatment prevents the formation of the allene product and favours the formation of the homopropargylic alcohol.



Scheme 19 Synthesis of homopropargylic alcohol from dioxazaborocanes by Frandrick and co-workers.[136]

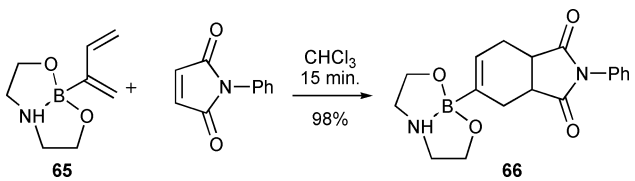
2.4.3. Dioxoazaborocanes and cycloadditions. Chiral induction has been performed in the cycloaddition of nitrile oxide with vinyl dioxazaborocanes **63** using chiral derivatives of diethanolamines (Scheme 20). Disubstituted isoxazolines **64** are obtained presumably after a 1,3-boratropic shift followed by protodeborylation.[138,139] Although the chiral induction remains moderate when the chirality is located α to the oxygen, better *ee*s are achieved when the chiral centre is borne by the third substituent



Scheme 20 Chiral induction in cycloaddition with vinyl dioxazaborocane.[138,139]

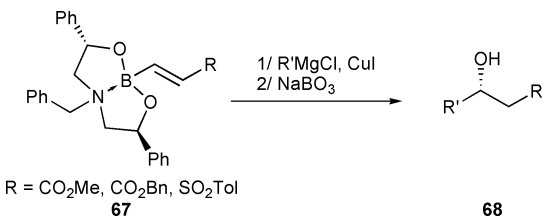
on nitrogen (**63** with $R^1 \neq R^2$). Nitrone–olefin cycloadditions have also been briefly investigated.

Boron-substituted 1,3-diene **65** has been proven to be an extremely reactive diene for the Diels–Alder reaction with *N*-phenylmaleimide. This reaction exhibits a $t_{1/2}$ of less than 4 min at −10 °C and provides **66** in 98% isolated yield at room temperature (Scheme 21).[140] In comparison, its potassium trifluoroborate counterpart requires 16 h at 100 °C to obtain 90% isolated cycloadduct.



Scheme 21 Enhanced reactivity in Diels–Alder reactions.[140]

2.4.4. Chiral auxiliaries in conjugate addition. The boron moieties of chiral vinyl dioxazaborocanes **67** have also been involved as chiral auxiliaries in the conjugate addition of *in situ* generated organocuprates, which after C–B bond oxidation provides optically active secondary alcohols **68** in moderate yields and medium to high enantioselectivities (Scheme 22).[141]



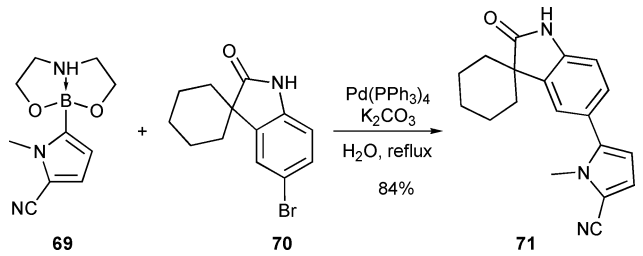
Scheme 22 Chiral auxiliaries in conjugated additions.[141]

2.5. Use in transition metal-catalysed reactions

2.5.1. Suzuki–Miyaura cross-coupling. There are only few examples of Suzuki–Miyaura cross-couplings using dioxazaborocanes, compared to those using boronic acids/esters or potassium trifluoroborates.

The cross-coupling of *N*-methyl-[96] and *N*-phenyl-pyridyl dioxazaborocanes[98,142,143] with halogenated derivatives has been reported with good yields. There is only one example of a solid-supported cross-coupling reaction. Stable *N*,*N*-diethylaminomethyl polystyrene-supported 2-pyridylboron reagent has been prepared and used in couplings with aromatic and heteroaromatic halides with good yields.[97] Hall and co-workers also used this type of polymer-supported reagent, but the free boronic acid was released prior to the cross-coupling reaction.[131,132]

A first example of a heterocyclic dioxazaborocane involved in a cross-coupling reaction was the 1-methyl-pyrrole-2-carbonitrile dioxazaborocane **69**. It was used as a coupling partner with **70** for the preparation of indolin-2-one derivatives **71** (progesterone receptors modulators) (Scheme 23).[81,144,145]



Scheme 23 Suzuki cross-coupling of 1-methyl-pyrrole-2-carbonitrile dioxazaborocane.[81]

We have recently reported a general method to access biaryl and aryl-heteroaryl compounds with a wide variety of functional groups from aromatic or heteroaromatic bromides and aryl dioxazaborocanes (Fig. 6).[146] Only one other aryl–aryl cross-coupling directly using a dioxazaborocane derivative had been detailed before this publication in a patent,[147] with a yield also similar to the one obtained with the free boronic acid. We showed in this work that the presence of water is required and that the addition of a copper salt exhibited a tremendous accelerating effect.

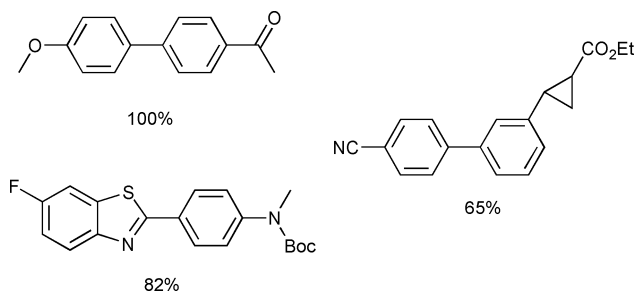
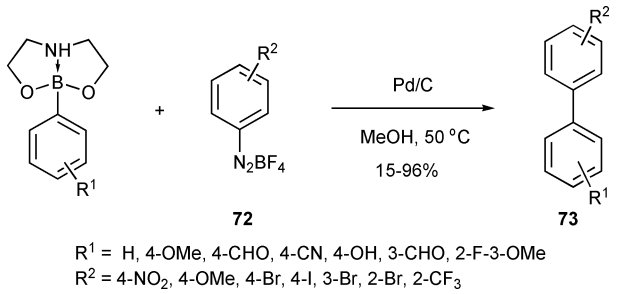


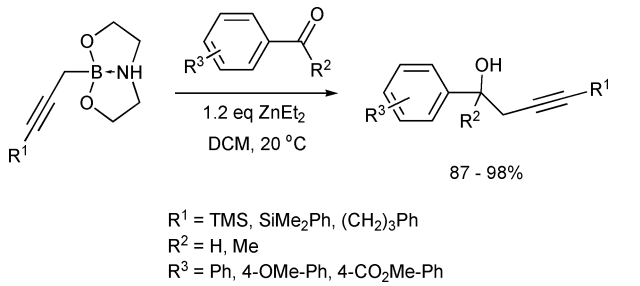
Fig. 6 Selected examples of Suzuki–Miyaura cross-coupling of aryl dioxazaborocanes with aryl or heteroaryl halides.[146]

We have also reported a more interesting application of the dioxazaborocanes in cross-coupling reactions. Their reaction with diazonium salts **72** without base at 50 °C provided quick and efficient access to biaryl systems **73** from easily isolated salts.[66] This work represented the first example of boronic esters cross-coupling with diazonium salts performed without additional basic salts (Scheme 24).

2.5.2. Zinc-catalysed propargylation. Following their work on the propargylation of aldehydes *via* the *in situ* generation of an "ate" complex, Fandrick and co-workers also reported the zinc-mediated propargylation of aromatic aldehydes and ketones with homopropargylic dioxazaborocanes (Scheme 25).[148] A boron–zinc exchange was employed to generate *in situ* propargylzinc intermediates. Better yields were obtained than with their first method highlighted above. High yields were obtained with both aldehydes and ketones, provided that 1.2 equivalents of diethyl zinc were used.

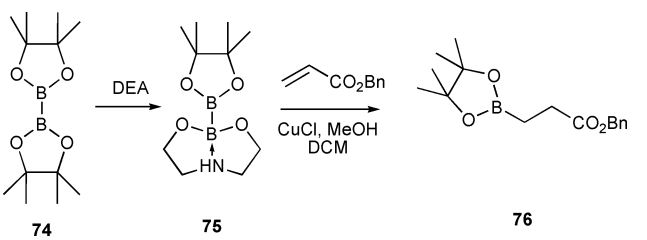


Scheme 24 First cross-coupling of aryl boronic esters with diazonium salts without the use of a base.[66]



Scheme 25 Synthesis of homopropargylic alcohols from homopropargylic dioxazaborocanes by Fandrick and co-workers.[148]

2.5.3. Boration of electron deficient olefins. The dioxazaborocane moiety has also been observed in the diboron derivative **75**, obtained by a single "transesterification" of bispinacolatodiboron **74** with diethanolamine (Scheme 26). This adduct has then been efficiently involved in a mild Cu(I)-catalysed β-boration of electron deficient unsaturated compounds.[149] Interestingly only the sp^2 hybridised boron seems to be transferred in this process.



Scheme 26 Mixed diboron compound featuring a dioxazaborocane moiety and its application in β-boration.[149]

Conclusions

As presented in this short review, dioxazaborocanes constitute an interesting family of boronic derivatives. They are exceptionally stable crystalline solids with high and sharp melting points, indicating a good thermal stability. Their synthesis is usually easy to carry out and high-yielding, and their purification by simple filtration is usually easy to set up, allowing the isolation of highly pure material. A wide array of dioxazaborocanes have been reported including aryl, heteroaryl, alkyl and alkenyl substituents at boron. Nevertheless, these compounds have essentially been made in order to fully characterise and isolate a boron intermediate. They were then generally hydrolysed back to the boronic acid or transesterified to a boronic ester. Only recently

has their direct use in organic reactions been reported. We believe that, as recently exemplified, a better understanding of their structure in solution will turn these compounds into an interesting alternative to the current stable boronic derivatives such as potassium trifluoroborates. This approach is currently under investigation in our group.

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